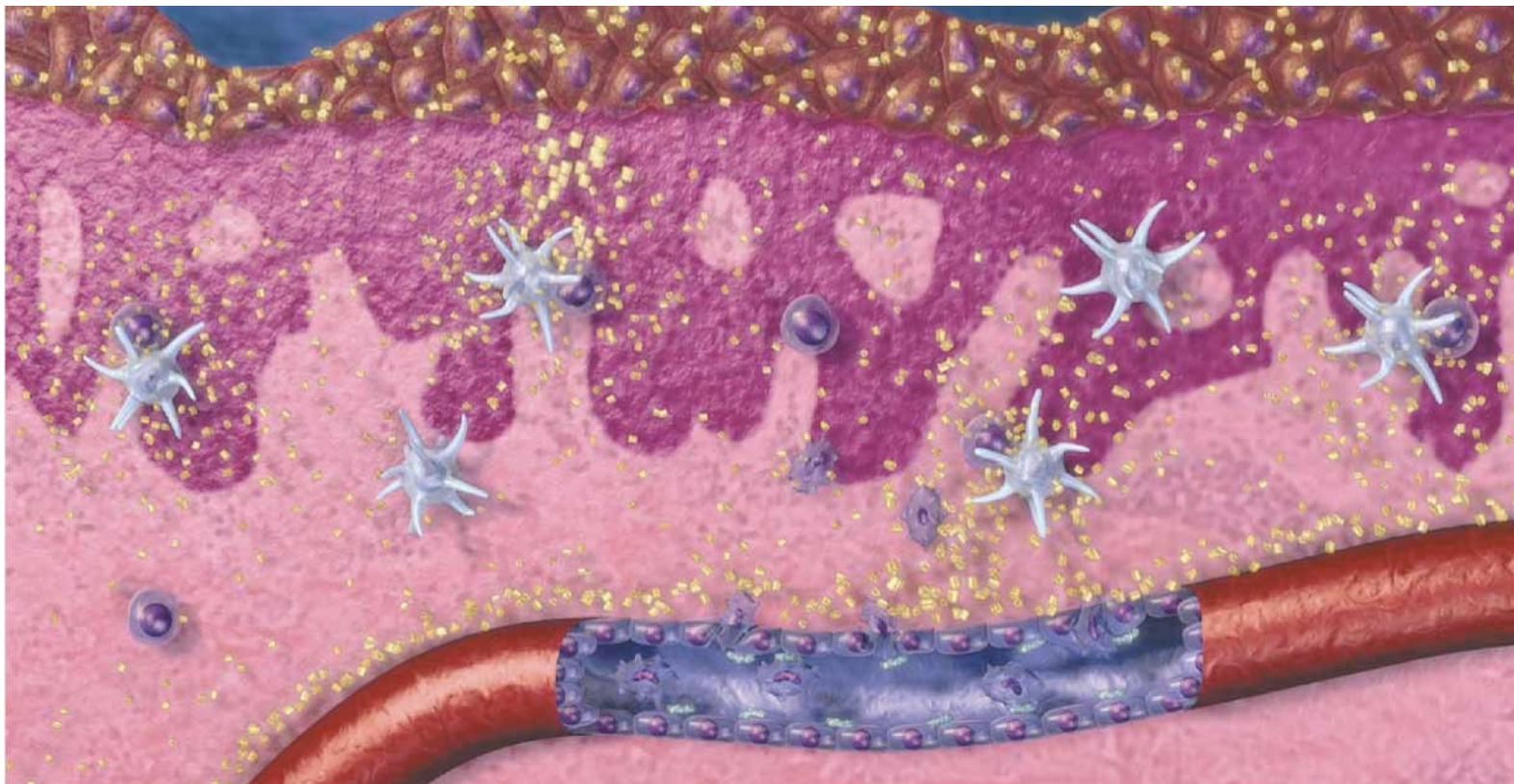


TNF Inhibition in the Treatment of Psoriatic Disease: New Findings in Clinical Research



The Role of TNF in Psoriasis: Untangling the Cytokine Web

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Professor of Microbiology and Immunology
Loyola University Medical Center

Newest Biologic Option for Psoriasis on the Horizon: Overview of U.S. Phase III Pivotal Trial Results

David M. Pariser, MD
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Global Long-Term Safety Update on Fully Human, Soluble Receptor TNF Antagonist

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CME Recognition

The SKIN & ALLERGY NEWS supplement, "TNF Inhibition in the Treatment of Psoriatic Disease: New Findings in Clinical Research" is recognized by the American Academy of Dermatology for 1 hour of AAD Category 1 credit and may be used toward the American Academy of Dermatology's Continuing Medical Education Award.

Term of approval: December 2003-November 2004.

This program was developed in accordance with the Accreditation Council for Continuing Medical Education guidelines.

Target Audience

This activity has been developed for dermatologists and other health care professionals involved in the treatment of psoriasis.

Educational Needs

Psoriasis is a common dermatologic disease that profoundly affects the lives of many patients. Those with mild disease often respond to well-tolerated topical medications. However, the treatments available for patients with moderate to severe disease are not always effective and are associated with serious systemic toxicity. The need for a more effective, less serious modality for managing patients has been at the forefront of research efforts in clinical dermatology. The discovery of the role of tumor necrosis factor (TNF) in psoriasis has allowed the development of anti-TNF treatments. One of these, etanercept, a patient-administered injectable medication, is currently approved by the U.S. Food and Drug Administration for the treatment of another TNF-mediated disease, rheumatoid arthritis. Etanercept has been used in clinical trials in patients with psoriasis. This activity updates dermatologists and other health care professionals who treat patients with psoriasis on the latest information concerning etanercept's mechanism of action, efficacy, and safety.

Learning Objectives

Upon completion of this activity, participants should be able to discuss:

- The role of tumor necrosis factor in psoriatic disease;
- What is currently known and proposed about the mechanism of action of TNF inhibition in the treatment of psoriasis;
- The clinical data currently available on the efficacy of etanercept in psoriatic disease;
- The safety issues relating to etanercept use and clinical data regarding safety.

Faculty Disclosure

Faculty/authors must disclose any significant financial interest or relationship with proprietary entities that may have a direct relationship to the subject matter. They must also disclose any discussion of investigational or unlabeled uses of products.

Dr. Gottlieb has received funding from Johnson and Johnson, XOMA LLC, Abbott Laboratories, and Ligand Pharmaceuticals Inc. She is a consultant to Novartis AG, Wyeth Pharmaceuticals, Eisai Inc., and Celgene Corporation. She has received research funding from and is a consultant to Amgen Inc., Biogen, Inc., CellGate, Inc., Centocor, Inc., Genentech, Inc., QUATRx Pharmaceuticals Company, and Schering-Plough Corporation. She has a financial interest in Telik, Inc. **Dr. Nickoloff** is a consultant to Amgen Inc. He discusses the investigational use of TNF-targeting agents in the treatment of psoriasis. **Dr. Pariser** has received clinical grants from Abbott Laboratories. He has received clinical grants from and is a consultant to Amgen Inc., Biogen, Inc., Centocor, Inc., and Genentech, Inc. He discusses the investigational use of etanercept in the treatment of moderate to severe psoriasis.

The Role of TNF in Psoriasis: Untangling the Cytokine Web

Brian J. Nickoloff, MD, PhD

The introduction of biologic treatments for immune-mediated inflammatory diseases has resulted in new lines of research into the pathogenesis of such diseases. Regarding psoriasis in particular, it is now known that several cytokines—especially tumor necrosis factor (TNF)—play a central role in this common and enigmatic skin disease.

Cytokine Network Theory of Psoriasis

The initial work on the cytokine network theory of psoriasis dates to 15 years ago, when this author began studies in Dr. Eugene Farber's Department of Dermatology at Stanford University, exploring how T cells and keratinocytes interacted. The next step was an exploration of TNF in cutaneous inflammation, followed by the role of TNF and TNF inhibitors in the psoriatic process. This work provided much of the scientific basis for the development of our concept of the immunopathogenesis of psoriasis, culminating in the cytokine network theory.

Foundation From Basic Scientific Research

Early in the history of this search for the molecular basis of a number of inflammatory diseases, the exploration of the modulators of adhesion molecule expression was begun. A particular target was the modulator that induced intercellular adhesion molecule 1 (ICAM-1), which in turn facilitated binding by leukocyte function-associated antigen 1-positive T cells. Once we identified this ligand receptor pair (which also functions in mediating the binding of T cells

to professional antigen-presenting cells), our search narrowed to cytokines that could modulate the expression of ICAM-1. This led to the identification of TNF, and, indeed, TNF was consistently found to be expressed by the dermal dendritic cells in psoriatic plaque tissue. In addition, it was established that other major sources of TNF are macrophages, keratinocytes, T cells, and mast cells.¹

“[I]t is now known that several cytokines—especially TNF—play a central role in [psoriasis].”

Simultaneously, in other lines of research in our laboratory and others, TNF emerged as being potentially important in cutaneous inflammation. We and others performed simple studies in allergic contact dermatitis reactions as well as studies involving repeated tape stripping of human skin designed to remove the stratum corneum. Sequential polymerase chain reaction studies

showed that, as early as 6 hours after stratum corneum removal (and barrier perturbation), elevation of TNF and other cytokines could be detected in the epidermal compartment.¹ Similar work done by several groups in murine models added support to the understanding that TNF is one of the primary cytokines in cutaneous inflammation.¹

Finally, early studies demonstrated that TNF combined with interferon- γ is highly synergistic in a variety of ways. For example, transcription of the chemotactic polypeptide interleukin 8 (IL-8), the monocyte chemoattractant and activity factor, and ICAM-1 is mild and transient when keratinocytes are exposed only to TNF. However, in the presence of TNF and interferon- γ , transcription levels are greatly exaggerated and highly persistent. This observation further supports the findings that cytokines, when combined, often produce dramatic synergistic responses in the skin.^{2,3}

Current Understanding of TNF and Cytokine Biology

Since the early work in TNF and cytokine biology, the field has greatly expanded. We have learned that not only does TNF

Table. Role of TNF- α in the Immunopathogenesis of Psoriasis

- TNF- α is elevated in psoriatic lesions.
- Elevated TNF- α levels lead to increased production of proinflammatory cytokines by T cells and macrophages.
- Dendritic cell activation is stimulated.
- Further T-cell activation occurs.
- Synthesis of adhesion molecules and chemotactic polypeptides by keratinocytes and endothelial cells leads to increased inflammatory cell infiltrates.
- Keratinocyte proliferation and resistance to apoptosis is also increased.

Source: Courtesy of Brian J. Nickoloff, MD, PhD.

influence keratinocytes, which were our first target cells, but TNF can have a variety of pleiotropic effects on a range of cell types, including keratinocytes, T cells, dendrocytes and blood vessels.

Initially, TNF was placed at center stage in the cytokine network theory for psoriasis.¹ We envisioned that both exogenous and endogenous stimuli would converge on the professional antigen-presenting cells, which could also be influenced by the role of the nervous system (including mast cells). Irrespective of the nature of the stimulus, production of TNF was portrayed as initiating a cascade of secondary events, including production of adhesion molecules, chemotactic polypeptides, and growth factors.

Later, the development of the severe combined immunodeficiency (SCID)-HU xenograft murine model of psoriasis allowed us to perform experiments in animal models. To understand the immunologic basis of psoriasis, grafts were made using immunodeficient mice—that is, SCID mice—that could not reject human skin. We found that psoriatic plaques could be created with injection of activated CD4+ T cells into

engrafted symptomless skin. These psoriatic plaques had all the clinical immunophenotypic and immunologic markers of those found in plaques removed from human patients with psoriasis. In addition, using the SCID-mouse model, we were also able to determine that if cytokine production was blocked (by using cyclosporine A), psoriatic plaques did not develop.

As a result of this work, we began to use treatments in patients with psoriasis that were targeted toward the end of reducing cytokine production, particularly focusing on blocking interferon- γ and TNF production.

Our current model of psoriasis (Figure) is one in which TNF is produced on stimulation in symptomless skin and can then influence a variety of cell types. We emphasize that, in this model, TNF can trigger the keratinocytes to produce adhesion molecules such as ICAM-1, as well as IL-8, monocyte chemoattractant and activity factor (MCAF), and various signal transduction elements that can amplify this inflammatory response. We also know that TNF can drive T cells to proliferate and, in fact, to produce interferon- γ .

TNF not only is produced by

dendritic cells, but also can influence further dendritic cell maturation and dendrocyte production. A molecule that must be further researched is an interferon-inducible protein called IFI 16 that appears to regulate the longevity of dendritic cells. Note that TNF can induce the adhesion molecules ICAM-1, vascular cell adhesion molecule, and E-selectin on endothelial cells to help draw more T cells into this mix. Finally, it has become clear that a number of agents targeting TNF are highly efficacious in psoriasis. By targeting one of the primary cytokines, such as TNF, it is reasonable to interrupt this vicious cycle and extinguish the fire that drives this chronic inflammatory process.

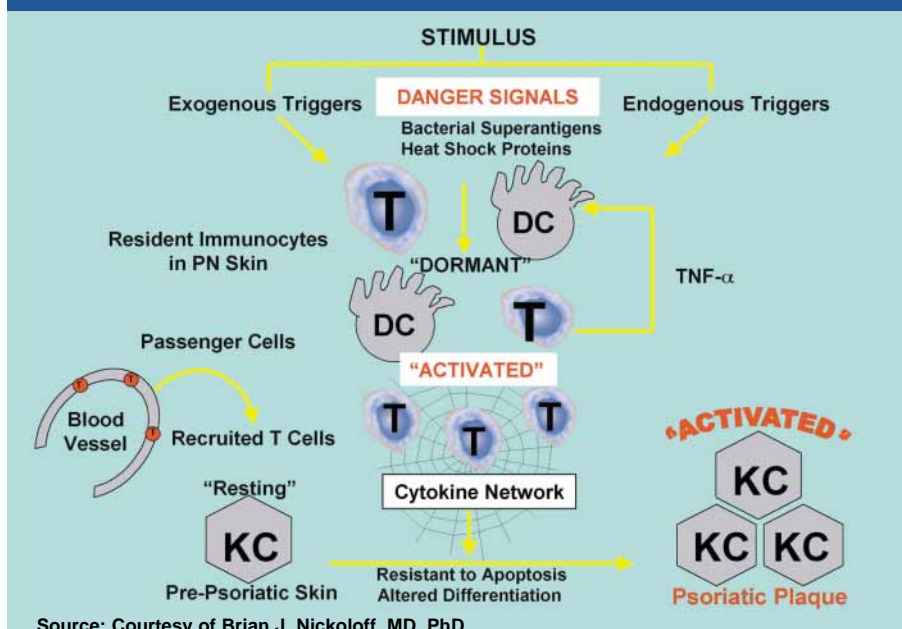
Conclusion

The current challenges in research rely on identifying why T cells and dendritic cells come together in the first place and produce TNF in psoriasis. In addition, initial triggering factors are now being sought that highlight endogenous mediators such as heat shock proteins that can bind to receptors (ie, CD91) on dendritic cells. This so-called danger signal activates the dendritic cells to produce TNF and initiates the cytokine cascade. Finally, we postulate that cytokines can activate keratinocytes to become resistant to apoptosis and alter their differentiation program, accounting for the accumulation of keratinocytes that produce thick, scaly psoriatic plaques.

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2. Piguet PF, Grau EG, Hauser C, Vassalli P. Tumor necrosis factor is a critical mediator in hapten-induced irritant and contact hypersensitivity reactions. *J Exp Med.* 1991;173:673-679.
3. Nickoloff BJ, Naidu Y. Perturbation of epidermal barrier function correlates with initiation of cytokine cascade in human skin. *J Am Acad Dermatol.* 1994;30:535-546.

Figure. Immunopathogenesis of Psoriasis: The Current View



Source: Courtesy of Brian J. Nickoloff, MD, PhD.

Newest Biologic Option for Psoriasis on the Horizon: Overview of U.S. Phase III Pivotal Trial Results

David M. Pariser, MD

The National Psoriasis Foundation reports that some 2 million Americans have plaque psoriasis that is classified as moderate to severe. Although patients with less severe psoriasis may be satisfactorily treated with topical medications, those with moderate to severe disease often must rely on systemic medications to control their symptoms. These medications are effective but highly toxic with long-term use.

The biologic agents that target tumor necrosis factor (TNF) hold great promise for patients with moderate to severe psoriasis. A U.S. pivotal trial of one of these agents, the fully human, soluble receptor anti-TNF agent etanercept, was completed recently, and the data are now available for review.

Study Design and Enrollment Criteria

The U.S. phase III pivotal trial of etanercept in patients with psoriasis included 652 patients in 47 centers. After appropriate screening and a washout period, patients were randomized to one of four treatment groups: the standard dosage of etanercept for rheumatoid arthritis [RA], juvenile RA, and psoriatic arthritis (25 mg twice weekly); twice the standard dosage of etanercept (50 mg twice weekly); half the standard dosage of etanercept (25 mg once weekly); or placebo for the first 12 weeks. There were no significant differences among patients in the randomized groups in any of the demographic parameters. The average Psoriasis Area Severity Index (PASI) score was 18.

The primary efficacy end point, 75% improvement in PASI (PASI

75), was measured at week 12, along with other efficacy variables—PASI 50, PASI 90, physician static global assessment, patient static assessment, and the Dermatology Life Quality Index (DLQI). The study was then carried out for another 12 weeks, for an accumulated 24-week assessment of safety and efficacy.

“Statistically significant differences [in PASI scores] were seen in all dosing ranges as early as 2 weeks after the start of the trial.”

The inclusion criteria included active, stable plaque psoriasis involving 10% or more of the body surface area (BSA) and a minimum PASI score of 10. In addition, patients were required to be at least 18 years of age and to have received previous systemic therapy or have been candidates for systemic therapy or phototherapy.

Exclusion criteria for this study were any previous exposure to etanercept or any other anti-TNF agent, or use of other investigational drugs, biologics, topical corticosteroids, or phototherapy within the previous 4 weeks.

Eighty-seven percent of patients receiving placebo and later etanercept completed the 24-week study, a remarkably high completion rate. The high subject retention rate may be attributed to the study design—the fact that patients were aware

that even if they were randomized to the placebo group for 12 weeks, they would receive the active drug at some point. There were no significant differences between the active treatment and placebo groups in withdrawals resulting from adverse events. Completion rates for the other dosage groups were 85% for those receiving etanercept 25 mg once a week, 87% for those receiving 25 mg twice weekly, and 92% for those receiving 50 mg twice weekly.

Primary End Point at 12 Weeks

The primary end point of PASI 75 was achieved by 4% of patients in the placebo group, 14% of patients who received etanercept 25 mg once weekly, 34% of those who received etanercept 25 mg twice weekly, and 49% of those who received etanercept 50 mg twice weekly. Thus, this study demonstrated a linear, dosage-related improvement in PASI 75, beginning at 25 mg once weekly, improving at 25 mg twice weekly, and reaching the greatest improvement at a dosage of 50 mg twice weekly. These differences are statistically significant, compared with baseline, with placebo, and with each other.

PASI 50 at 12 weeks was achieved by 58% of the group who received etanercept 25 mg twice weekly, and by 74% of the patients who received 50 mg twice weekly. Twenty-two percent of patients achieved PASI 90 in the 50-mg, twice-weekly group, 12% of patients who received etanercept 25 mg twice weekly achieved PASI 90, and among those who received etanercept 25 mg once a week, 3% achieved PASI 90. Statistically significant

differences were seen in all dosing ranges as early as 2 weeks after the start of the trial.

During the second 12-week period, all patients continued on the dosage to which they were originally randomized, except for the patients who were originally randomized to the placebo group. Those in the latter group were given etanercept at the standard dosage, 25 mg twice weekly.

Improvements in Other Efficacy Variables

Improvements were seen in the physician static global assessment, the so-called snapshot in time, or the clinical impression of patient appearance (achievement of clear or almost-clear status) at a given visit, but not compared with appearance at other visits. These results are virtually identical to those seen for PASI 75,

in terms of dose relationship and the fact that the placebo group caught up with their cohorts by the end of the study. The patient

“The primary end point of PASI 75 was reached by 49% of patients who received etanercept 50 mg twice weekly.”

static global assessment showed the same dose relationship and closely paralleled the findings on the physician static global assessment. The mean change in DLQI scores supported the other findings in terms of a dose relationship.

Good Safety Profile

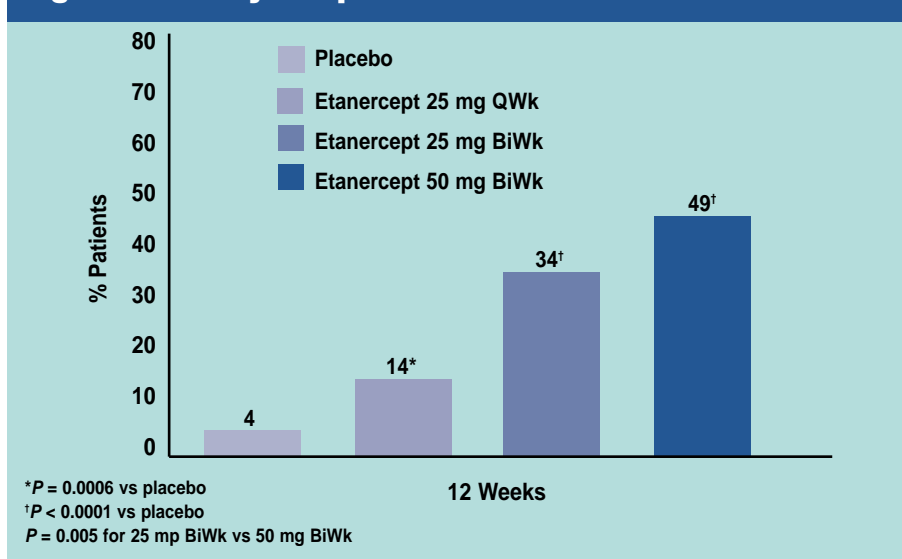
A general discussion of safety with the use of etanercept is provided in the article by Alice B. Gottlieb, MD, PhD (page 8). In this particular study, no trends were seen in adverse events between the active treatment and placebo groups except for injection-site reactions. This is a macular dermatitis that is commonly associated with etanercept. Except for its appearance, the reaction is typically asymptomatic, short lived, and self-limited. If necessary for patient comfort, topical hydrocortisone may be applied. This was the only adverse event that occurred in more than 5% of patients.

Conclusion

The U.S. phase III pivotal trial of etanercept in patients with psoriasis showed that this drug is well tolerated and safe, with mild, self-limited injection-site reactions being the most common adverse event. This safety profile was maintained throughout 24 weeks of the trial.

The primary end point of PASI 75 was reached by 49% of patients who received etanercept 50 mg twice weekly. In addition, compared with baseline, statistically significant improvements in PASI, patient global assessment, and DLQI were noted at week 2, indicating that etanercept has a rapid onset of action in patients with psoriasis.

Figure. Primary Endpoint: Week 12 PASI 75



Global Long-Term Safety Update on Fully Human, Soluble Receptor TNF Antagonist

Alice B. Gottlieb, MD, PhD

Etanercept was approved in 1998 for the treatment of rheumatoid arthritis (RA). Since that time, it has been approved for the additional indications of juvenile RA and, most recently, psoriatic arthritis (PsA). Phase III clinical trials in psoriasis have been completed, and David M. Pariser, MD, provides an overview of the results on page 6 of this supplement. The safety and adverse event profile of etanercept have been established over 9 years of use worldwide—almost 6 of those years since the date of first marketing—for an accumulated experience in 150,000 patients and more than 230,000 patient-years.

Of greatest concern to physicians who consider anti-tumor necrosis factor (TNF) therapy in general is the potential increased risk for opportunistic infections, malignancy (including lymphoma), and the development of antinuclear antibodies. Other concerns are a history of demyelinating disorders and congestive heart failure. A particular concern is safety in children. In this article, the safety data specific to etaner-

cept will be addressed. Most of these data are from patients who have been treated for RA.

Local Reactions Most Common Adverse Event

The most common adverse event seen with etanercept is injection-site reactions. Local

“In the clinical trials of patients with RA, injection-site reactions were seen in 37% of cases....[which] is higher than what has been seen in the clinical trials in patients with psoriasis....”

reactions, which occur early in treatment, are typically mild, last for only a few days, and generally almost never require treatment. When treatment is

required, cold-water soaks and applications of over-the-counter hydrocortisone 1% cream are usually all that are needed to resolve the problem.

In the clinical trials of patients with RA, injection-site reactions were seen in 37% of cases.¹ This rate is higher than what has been seen in the clinical trials in patients with psoriasis, which ranged from 13% to 20%. The difference may be due to the fact that many patients with RA have pathergy and increased hypersensitivity (depending on their human leukocyte antigen type). Thus, it is possible that the population of RA patients demonstrated a rate of local reactions that is higher than what eventually will be seen as larger numbers of patients with psoriasis are treated.

Other commonly reported adverse reactions in the RA clinical trials are shown in **Table 1**.

Low Risk for Opportunistic Infections

Because of the nature of TNF activity—innate and adaptive immunity—there is some concern that etanercept might increase the risk for opportunistic infections, particularly tuberculosis. Indeed, experiments in TNF-knockout murine models indicate that mice without TNF cannot form granulomas.

To date, a total of 19 cases of tuberculosis have been reported since etanercept was approved for marketing. Over the same time period, the expected number of cases in the United States general population was 13 (although the expected tuberculosis rate in the population of patients with RA, in particular, is unknown). Most

Table 1. Adverse Events in RA Trials

Etanercept Adverse Events (AE)* % of RA Patients Reporting AEs in Controlled Clinical Trials		
EVENT	ETANERCEPT (n=349)	PLACEBO (n=152)
Injection site rxs	37	10
Infection		
Non-URI	38	32
URI	29	16
Headache	17	13
Nausea	9	10
Rhinitis	12	8

* Package Insert
RA = rheumatoid arthritis; rxs = reactions; URI = upper respiratory infection

of these 19 cases (52%) had extrapulmonary but localized disease, and 16% had disseminated (miliary) disease. None of the cases in the etanercept-treated patients was temporally related to the initiation of treatment. In the RA trials, tuberculin skin testing was not required. In addition, no cases of tuberculosis reactivation occurred in patients who did have a positive purified protein derivative (PPD) test or a clinical history of tuberculosis. Currently, etanercept is the only anti-TNF agent that does not carry a black-box warning regarding tuberculosis in its labeling.

Regarding patients with human immunodeficiency virus (HIV) who have a positive sputum culture for tuberculosis, 16 such patients were enrolled in the phase III psoriasis trials and were randomized to receive standard care plus placebo or etanercept, 25 mg twice weekly for 4 weeks. Etanercept did not interfere with the response to treatment for pulmonary tuberculosis, measured clinically, on x-rays, or sputum microscopy or culture. Interestingly, compared with controls, the patients on etanercept experienced a 25% increase in CD4+ counts by week 4, for reasons that were not apparent.

Low Risk of Malignancy in Patients With Psoriatic Disease

Some question has been raised regarding the potential increased risk for malignancy—specifically, lymphomas—with anti-TNF therapy. In the controlled trials of etanercept (most of which have been, as noted, in patients with RA), the observed number of lymphomas was 5 in the controls, with an expected incidence of 3.57.¹ Among the patients treated with etanercept, the expected incidence was 8.8, and the observed incidence was 11.¹ However, RA itself is associated with a two-fold increase in lymphoma,

Table 2. Etanercept Safety in Children

- **Open-label extension (n=58)**
 - **Most adverse events were of mild to moderate intensity.**
 - **No significant increases in the overall rates of adverse events or infections occurred with prolonged exposure to etanercept.**
 - **Types and rates of infection were similar to placebo group in the initial, double-blind study.**
 - **3 patients contracted varicella.**
 - **1 patient receiving other immunosuppressive therapy had complicated sepsis.**

Source: Lovell DJ, et al. *Arthritis Rheum.* 2003;48:218-226.

compared to the general population. Thus, any increase in lymphoma risk with etanercept, if one does exist, is probably quite small.

TNF-Targeting Drugs in Patients With Multiple Sclerosis

Rare cases of multiple sclerosis have been reported in patients who have taken etanercept. The total expected number was 12, the observed number was 14. For optic neuritis—a cardinal sign of multiple sclerosis—7 cases were expected and 9 observed.

In 12 cases of patients with severe RA who experienced demyelination and whose rheumatoid disease was so severe it was felt that rechallenge was warranted, 9 who were rechallenged had negative results. Nevertheless, it is this author's opinion that, in general, use of any TNF-targeting drug is inadvisable in patients with multiple sclerosis.

Antinuclear Antibodies and Lupuslike Conditions

Antinuclear antibodies were seen in about 11% of etanercept-treated versus 5% of placebo-treated subjects, in clinical trials with a population consisting mostly of patients with RA. Symptoms are exceedingly unlikely to occur as a result of the presence of antinuclear antibodies. If lupuslike symptoms do occur while patients are taking etanercept, resolution of these problems can be expected on cessation of therapy. The symptoms of lupuslike

conditions in such patients are arthralgias, minor skin involvement, and polyserositis—that is, not central nervous system or renal lupus, but rather a lupus pattern that is similar to what is seen when the condition is drug induced or that is more common in geriatric patients.

Cardiac Outcomes in Anti-TNF Studies

Some confusion exists regarding the effect of anti-TNF therapy on the risk for congestive heart failure (CHF). This arose from two clinical studies that were conducted to determine whether TNF-targeting drugs—specifically etanercept—would improve outcomes in patients with CHF. These studies were discontinued because of lack of efficacy. In one study, there was a trend toward worse cardiac outcomes in patients with existing CHF. Although there was no evidence that etanercept treatment causes CHF, the package labeling carries a precaution that patients with CHF who receive this drug should be carefully monitored.

Safety in Children

Etanercept is the only biologic agent approved for juvenile RA in children 4 years of age or older. In a double-blind study of etanercept versus placebo in children 4 to 17 years of age with juvenile RA, there was no difference in the frequency of adverse events or laboratory abnormalities between patients who received etanercept and

those who received placebo. In addition, no patient had persistent elevation of autoantibodies or developed an autoimmune disease. In the open-label extension with 58 patients (Table 2 on page 9), the adverse events were of mild to moderate intensity. There was no increase in infection with prolonged exposure, except that three children contracted varicella (which is not surprising, given the age of the population). One patient who received other immunosuppressive therapy did have complicated sepsis; however, it is not uncommon for rheumatologists to see sepsis in patients with juvenile RA who are taking multiple immunosuppressants.

Hematologic Events

A small number of patients with RA were found to have bone marrow hypoplasias (pancytopenias, anemias, or low platelet counts) while using etanercept. As a result, the drug's label carries a warning about hematologic events. However, it

is important to note that most of these patients were on concomitant therapy with other drugs, such as cyclophosphamide, and

“...RA itself is associated with a twofold increase in lymphoma, compared to the general population. Thus, any increase in lymphoma risk with etanercept, if one does exist, is probably quite small.”

some may have had Felty's syndrome, which, in itself, is associated with cytopenia. To date, such hematologic problems have not been seen in patients with psoriasis or PsA on etanercept therapy.

Conclusion

More than 9 years of experience in patients with RA has established the risk-benefit profile of etanercept. This is a category B drug, so unlike many of the treatment options for psoriasis, when needed, it may be given during pregnancy. Patients with active heart failure, demyelination, and serious infections such as pneumonia should not be treated with any anti-TNF biologic agents. The data are robust, however, showing that etanercept is safe and effective for long-term use and that it has not been shown to be associated with target organ toxicity. The anti-TNF biologic agents offer the first hope for safe and effective long-term management of a variety of immune-mediated inflammatory diseases, including RA, juvenile RA, psoriasis, and PsA.

Reference

1. Data on file, Amgen Inc., Thousand Oaks, Calif.

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CME Post-Test and Evaluation

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INSTRUCTIONS: For each question or incomplete statement, one answer or completion is correct. Six of 8 correct responses are required for credit. Circle the most appropriate response.

- The fully human, soluble protein anti-TNF agent:
 - Has shown benefit in some patients with congestive heart failure who also have rheumatoid arthritis.
 - Can be given to children down to 4 years of age.
 - Is likely to cause congestive heart failure.
 - Is likely to cause lupuslike symptoms.
- The concept of the immunopathogenesis of psoriasis developed by Nickoloff and colleagues is known as the _____.
 - Adhesion molecule hypothesis
 - Cytokine network theory
 - Cutaneous inflammation theory
 - Tumor necrosis factor hypothesis
- All of the following are major sources of tumor necrosis factor except:

a. ICAM-1	c. Mast cells
b. Keratinocytes	d. T cells
- As a result of work with the SCID-mouse model, treatments for psoriasis in humans began to be focused on blocking:
 - Adhesion molecules
 - CD4+ cells
 - Chemotactic polypeptides
 - Interferon- γ and tumor necrosis factor
- A molecule that appears to regulate the longevity of dendritic cells is known as _____.

a. E-selectin	c. IFI-16
b. ICAM-1	d. VCAM
- The primary efficacy end point in the phase III United States pivotal trial of etanercept was:
 - Dermatology Life Quality Index
 - 50% improvement in the Psoriasis Area Severity Index
 - Patients' static assessment
 - 75% improvement in the Psoriasis Area Severity Index
- The achievement of 75% improvement in the Psoriasis Area Severity Index in the phase III United States pivotal trial of etanercept:
 - Was seen in all groups, in a linear, dosage-related relationship.
 - Was seen in the groups who received the standard dosage and twice the standard dosage, but not in the group who received half the standard dosage.
 - Was seen only in patients who also had at least a 75% improvement in the patients' static assessment.
 - Was seen only in the group who received 50 mg twice weekly.
- Patients with psoriasis who are being considered for treatment with the fully human, soluble receptor TNF antagonist should:
 - Be cautioned about the possibility of severe allergic local reactions.
 - Be warned that the risk for lymphoma is fourfold, compared to the general population.
 - Have a negative PPD test before starting treatment.
 - Have a test for bone marrow hypoplasias prior to initiating therapy.

PROGRAM EVALUATION

We would appreciate your answering the following questions in order to help us plan for other activities of this type.

- How would you rate the clarity of the presentation of the material?
(Please check one)

	Excellent	Good	Fair	Poor
Text	_____	_____	_____	_____
Images	_____	_____	_____	_____
Post-Test	_____	_____	_____	_____

- How would you rate the clinical relevance of the material?

- How would you rate this material, compared with similar independent study presentations in print form?

- Was this a fair and balanced presentation? Please comment on the scientific rigor, fairness, and balance of the material.

- Do you believe such materials, supported by educational grants from industry, are appropriate and useful? Please rate from 0 (not appropriate/useful) to 10 (very appropriate/useful).

- What topics would you find useful for future programs?

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